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Cardiovascular Responses Elicited By Electrical Stimulation of the Hypothalamus

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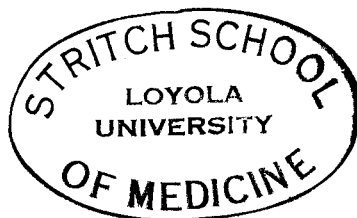


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**CARDIOVASCULAR RESPONSES ELICITED BY ELECTRICAL
STIMULATION OF THE HYPOTHALAMUS**

by

John W. Manning, Jr.



**A Dissertation Submitted to the Faculty of the Graduate School
of Loyola University in Partial Fulfillment of
the Requirements for the Degree of
Doctor of Philosophy**

June

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TABLE OF CONTENTS

Acknowledgments.....	11
Biography.....	111
Introduction.....	1
Materials and Methods.....	9
Stereotaxic Technique.....	9
Stimulating Parameters.....	13
Recording Technique.....	16
Experimental Procedure.....	19
Analysis of Data.....	20
Experimental Results.....	23
Augmentation, Acceleration, and Vasoconstriction Elicited by Hypothalamic Stimulation.....	23
Drug Effects on Vasonotor Responses.....	39
Discussion and Conclusions.....	43
Summary.....	48
Bibliography.....	49

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BIOGRAPHY

John William Manning, Jr. was born in New Orleans, Louisiana, on November 14, 1930. He received his elementary education in the parochial school system of New Orleans and graduated from Jesuit High School of New Orleans in 1947.

The same year he enrolled in the College of Arts and Sciences of Loyola University of the South. He pursued a course of study with a major in biology and a minor in chemistry and was awarded a Bachelor of Science degree in 1951.

In January 1952, he was employed by Tulane University in the Department of Physiology as a research assistant. This position he held until he was promoted to research associate in 1953.

He was married to Cynthia Satterlee in January 1954. This same month he entered a program of graduate study toward a degree of Master of Science in Physiology at Tulane University. He was awarded said degree in June, 1955.

In June of 1955 he took a position as research associate in the Department of Ophthalmology at Tulane University. On November 23 of this year, a baby girl, Kathleen, was born to Cynthia and John Manning.

In September, 1956, he moved to Chicago to begin a program of study towards a degree of Doctor of Philosophy at Loyola University and has to date been fulfilling requirements for this degree. A second child, Michael, was born on May 5, 1958.

INTRODUCTION

Early clinical observations of individuals with central nervous system lesions that involved the hypothalamus suggested this structure as an area in the brain that exerts control over the autonomic nervous system (1). The experimental physiology of the hypothalamus began with the work of Karpus and Kreidl (2,3,4,5,6, & 7). These authors stimulated the hypothalamic area electrically in cats and monkeys using needle electrodes. They found that many autonomic responses occurred following electrical excitation of various points in the hypothalamus. These responses included: dilatation of the pupil, changes in heart rate, defecation, salivation, contraction of the bladder, contraction of the nictitating membrane, and rises in arterial blood pressure. It was further shown that these responses could be obtained in the chronic decorticate preparation and were limited to the hypothalamic portions of the diencephalon (7). From these anatomical and physiological data, the authors established the hypothalamus as a subcortical area that exerts control over the activities of the autonomic nervous system.

The observations of Cannon and co-workers (8,9, & 10) on acute decorticate animals suggested that the diencephalon was essential for activation of the adrenal medulla during the sham rage response. During the rage state these animals showed a widespread sympathetic activation.

If a transection was then made just caudal to the inferior colliculi, the response of the adrenal medulla failed to occur.

Further evidence that would suggest the diencephalon as the subcortical area responsible for the rage reaction seen in the decorticate animal is afforded by the work of Woodworth and Sherrington (11) and Bazett and Penfield (12). These authors showed that, in the chronically decerebrate cat, the sympathetic nervous system could be activated reflexly by strong afferent stimulation. The somatic and visceral responses elicited were different in degree and direction for the midbrain preparation as compared to that seen in the decorticate preparation.

Bard, at the suggestion of Cannon, undertook a study to determine the subcortical areas responsible for sham rage. Bard's extensive observations in the acute decorticate cat permitted him to relate the somatic and visceral activity of the rage state to central mechanisms confined within the caudal half of the hypothalamus and the more ventral and more caudal portions of the thalamus (13 & 14). He concluded that the hypothalamus represents a center for the activation of sympathetic reactions. The results of hypothalamic stimulation have given support to this conclusion.

Ranson and his co-workers (15,16,17,18, & 19) made a comprehensive mapping of reactive areas within the hypothalamus of the anesthetized cat using a stereotaxic instrument for more accurate positioning of the stimulating electrodes. The responses elicited were similar to those noted by Karplus and Kreidl and consisted of a rise in blood pressure,

increased rate and amplitude of respiration, dilatation of the pupil, and contraction of the bladder. These responses did not always occur concomitantly and were generally complex. Depending on the point stimulated and the strength of stimulus, one or more types of response were obtained.

The latent period of the blood pressure rise following stimulation was approximately one second. Such a short latency suggested a neural rather than a hormonal mediation between the site of stimulation and the effector organ. In fact, Karplus and Kreidl (7) were able to evoke a rise in blood pressure by hypothalamic stimulation after the adrenal glands and hypophysis had been removed. That hypothalamic stimulation could increase the activity of the adrenal medulla was recognized by early workers (20,21, & 22). Recent evidence suggests that the hypothalamus may influence not only the amount of hormones released; but also the ratio in which the two hormones (epinephrine and norepinephrine) of the adrenal medulla are released (23,24, & 25). Thus, for a rise in blood pressure to be mediated by a nervous mechanism following adequate hypothalamic stimulation, there must be a short latency in the onset of the response.

In the work of Ranson and co-workers great detail was given to the anatomical site of stimulation and the associated fiber tracts and nuclei involved. For the purpose of this report, it will suffice to describe briefly those areas which gave marked changes in blood pressure upon stimulation.

Moving rostro-caudally through the hypothalamus, few pressor points are obtained until a plane at the level of the posterior border of

the optic chiasma is reached. There is then a sudden increase in the number of active points. From this level to a section through the caudal portion of the mammillary bodies, numerous points are found that give a marked rise in blood pressure. Their distribution is diffuse and includes the areas of the lateral hypothalamus, the median forebrain bundle, a strip adjacent to the ventricular wall, the caudal portions of the posterior hypothalamic nuclei, and the fields of Forel. Few or no pressor points were obtained from the thalamus, the subthalamic nuclei and the dorsomedial hypothalamic area. In general, these data agree with those obtained by other investigators working with both cats and dogs (26,27, & 28).

Hess (26 & 29), by means of chronic implanted electrodes, stimulated the hypothalamus of the unanesthetized cat. It was his observation that the various autonomic responses evoked were located in relatively confined areas. There was an overlapping of the areas and the responses were not confined to anatomical nuclei. From a comprehensive study, he concluded that in the medial and posterior part of the diencephalon are found these autonomic responses that are mediated by the sympathetic nervous system. The parasympathetic nervous system is represented in the anterior part of the hypothalamus. It is apparent from the above studies that an anatomical description of a point of stimulation serves only to give a precise location and not a localization of a functional center that is co-extensive with a histological nucleus.

The efferent paths from the hypothalamus to the intermediolateral cell column and sympathetic centers of the spinal cord may be divided into

two principle pathways (30). Fibers of the periventricular system arise throughout the hypothalamus, with a large number of fibers contributed by the posterior hypothalamus. The periventricular system continues caudalward in the central gray as the dorsal longitudinal fasciculus (31). The work of Beattie, Brow and Long (32 & 33) suggests that some of these fibers enter the midbrain tegmentum, but that the majority of fibers descend in the medial longitudinal fasciculus. Physiological data from cats with various sections in the lower brainstem does not support this conclusion. Instead, the diffuse descending connecting system, which is a caudal extension of the medial forebrain bundle scattered in the lateral reticular formation of the brainstem, is more important in the transmission of hypothalamic impulses to lower sympathetic centers (34 & 35).

From the preceding description and other literature (36,37, 38,39,40, & 41), there exists a large body of evidence to establish the hypothalamus as an important subcortical area associated with autonomic function. The work of Hess and others (42,43, & 44) gives evidence for a functional division of the hypothalamus. The parasympathetic nervous system is represented in the anterior hypothalamus, while the sympathetic system is represented in the posterior division. The efferent outflow from the hypothalamus to lower brainstem autonomic centers and the spinal cord is not known in detail, but must involve portions of the lateral reticular formation.

The recent work of Gellhorn and his associates (45,46, & 47) suggests that the hypothalamus exerts a tonic and phasic control on blood

pressure and heart rate. On the basis of studies in animals with lower brain stem transections (11,48,49, & 50), this view is in contrast to the classic teaching that the medullary centers mediate tonic and reflex control of the blood pressure and heart rate (51).

According to Oellhorn, if the posterior hypothalamus is depressed by intrahypothalamic injections of drugs or is destroyed by electrolytic lesions, a small fall in blood pressure and a slight slowing of the heart rate occur. After such a procedure the reflex response to a hypotensive agent (histamine or acetylcholine) is greatly depressed. These results are believed to be due to the loss of the sympathetic division of the hypothalamus. On the other hand, if the anterior hypothalamus is depressed or destroyed, there results a slight rise in mean arterial pressure and heart rate. Under these conditions, the reflex response to hypertensive agents (nor-epinephrine) is depressed. Further evidence is given to show that a reciprocal inhibitory innervation exists between the anterior and posterior hypothalamus (52 & 53).

The activation of the sympathetic outflow to the heart by reflexes, by direct stimulation of the sympathetic trunk, or by stimulation of the lower brainstem results in an augmentation in the force of myocardial contraction (54,55,56,57,58,59,60, & 61). These data emphasize the significance of a nervous control over the force of myocardial contraction. It was further noted that a differential response is obtained when the isolated left stellate ganglion is stimulated as compared with stimulation of the right stellate ganglion (56). The predominant effect elicited from

the left side was cardioaugmentation, while that from the right side was a cardioacceleration with little cardioaugmentation. This differential response was attributed to the site of termination of sympathetic fibers on the heart, that is, a differential ending of postganglionic fibers on nodal and muscle tissue.

The cardiovascular responses to hypothalamic stimulation, with few exceptions, have been reported previously as changes in mean arterial pressure or as pressor and depressor responses. The inadequacy of recording techniques employed by early investigators did not allow for an accurate analysis of pulse pressure changes. Thus, no interpretation of changes in myocardial contraction could be made. Moreover, the reported changes in heart rate were not necessarily due to direct activation of sympathetic outflow to the heart. In many reports the heart rate was measured by direct palpation for 30 seconds before and during stimulation. Usually, the vagi were left intact. Thus, accelerator responses could be accounted for by central inhibition of tonic vagal discharge and/or activation of the adrenal medulla. Other investigators have used the electrical activity in the inferior cardiac nerve as an index of sympathetic acceleration of the heart (41). However, simultaneously obtained pressure pulse records show no change in either heart rate or pulse pressure. The use of barbiturate anesthesia is probably another source of discrepancy seen in the earlier literature, since it has been shown that the hypothalamus is depressed by barbiturates (27).

In the literature, there exists no clear cut evidence that

hypothalamic areas exert direct sympathetic control over the heart rate and/or the force of myocardial contraction. Recent studies from this laboratory (61 & 62) on bulbar regulation of cardiovascular function have failed to corroborate the existence of a sympathetic cardioaccelerator center in the dorsal reticular formation of the medulla. Therefore, it is the purpose of this thesis to demonstrate and to analyze the cardiovascular responses elicited by electrical stimulation of the hypothalamus. By the accurate recording of the arterial pressure pulse, changes in the dynamics of the heart may be interpreted from alterations in the pressure pulse. The changes that occur with short latencies in the vagotomized animals following stimulation would be the result of direct sympathetic activation of the heart. It is further proposed to show the effects of certain anesthetics on the activity of these hypothalamic areas.

MATERIALS AND METHODS

1. Stereotaxic Technique

Stereotaxic procedure was used to implant the stimulating electrodes into the diencephalon through a small hole in the cat's cranium. This method permits access to all areas within the cranium with a minimum of tissue damage.

Horsley and Clarke (63) first employed the stereotaxic method to study the functional aspects of the central nervous system. Clarke is credited with the conception and design of the stereotaxic instrument.

"According to Ernest Sachs, the only living neurosurgeon trained by Sir Victor Horsley and the first to bring the stereotaxic instrument to the United States ('11), Clarke was responsible for the idea of a stereotaxic instrument. The idea was said to have been conceived in Egypt when Clarke was recovering from pneumonia which resulted from aspiration of an aspirin tablet. On returning to Britain, Clarke presented his idea to Horsley who was favorably impressed. James Swift of London constructed the first model and many subsequent modifications. The remaining years of Clarke's life, as well as his savings, were spent developing stereotaxic instruments and methods. It was his

hope even at that time that stereotaxic technique would prove useful in human neurosurgery. (See Sachs and Fincher, '27)."¹

The stereotaxic instrument is simply a three dimensional carriage which can be mechanically manipulated in relation to established reference planes. The reference planes are determined by anatomical structure of the skull. They are:

1. A horizontal zero plane that is ten millimeters dorsal to the interaural line between the external auditory meati,
2. A mid-sagittal zero plane, and
3. A frontal zero plane which is perpendicular to the horizontal plane and which passes through the interaural line.

The three intersecting reference planes are at right angles to each other and permit the localization of neural structures within the brain in reference to the zero planes. The stereotaxic coordinates of a neural structure are then measured in millimeters to the right or left, above or below, and caudal or rostral to the intersection of these reference planes.

Blunt point concentric bipolar stimulating electrodes were employed in this study. The reference electrode was 22 gauge hollow tubing completely insulated except for the terminal ring tip. An

¹Carpenter, M. B. and Whittier, J. R. "Study of Methods for Producing Experimental Lesions of the Central Nervous System with Special Reference to Stereotaxic Technique". J. Comp. Neurol., 97: 75, 1952.

insulated stainless steel wire was inserted into this tubing so as to project approximately one millimeter beyond the terminal ring. The insulation was removed from approximately 0.5 millimeters of the tip of the stainless steel wire (active electrode). The integrity of the insulation was routinely tested.

Histological verification of the point of stimulation was made from serial sections of the brainstem. Microscopic determination of the fiber tracts and associated nuclei in the area of stimulation was made. Because of the time involved in the preparation of tissue for sectioning, the histological data is not complete. Figure 1 is a section through the caudal posterior hypothalamic nuclei. Four electrode paths are seen in this figure.



FIGURE 1

A 4X photographic enlargement of a cross-section through the cat's diencephalon showing four electrode paths.

2. Stimulating Parameters

Electrical stimuli were delivered from a Simpson square wave generator. The frequency, intensity, and duration of the stimulating pulse was controlled and was continuously monitored by an oscilloscope built into the stimulator and connected in parallel with its output.

Relatively little data exist that would dictate the optimal stimulating parameters in order to obtain cardiovascular responses from the brainstem, and in particular, from the hypothalamus. Although it has been shown that a pressor response may be converted into a depressor response simply by reducing the frequency of stimulation (41 & 44); it was concluded that the magnitude of the pressor response increased with frequencies up to several hundred cycles per second. It must be pointed out that these workers fail to report their stimulating pulse duration. Further, their methods of recording the cardiovascular responses were inadequate to permit an accurate analysis of possible augmentation of myocardial function.

Recent data from this laboratory (62), using a pressure pulse recording technique, demonstrated that the type of cardiovascular response obtained with lower brainstem stimulation was a function of the three stimulation parameters. It was concluded from this study that the duration of the stimulation pulse is one of the critical factors controlling the activation of fibers in this area.

In view of this evidence, the parameters selected for stimulating the hypothalamus were a duration of 2 milliseconds, a frequency of 70 cycles per second, and a voltage between 2 to 7 volts.

In order to test the suitability of these parameters, for the hypothalamus, an active point in the posterior lateral hypothalamus was found. Stimulation of this point produced an elevation in systolic and diastolic pressures with a marked rise in the pulse pressure and in the pulse rate. The control values were a systolic pressure of 108 mm. Hg., diastolic pressure of 90 mm. Hg., a pulse pressure of 18 mm. Hg., and a heart rate of 145 per minute. Following stimulation the values were elevated to a systolic pressure of 230 mm. Hg., diastolic pressure of 160 mm. Hg., a pulse pressure of 70 mm. Hg., and a heart rate of 182 per minute. The parameters of stimulation were 4 volts, a 2 millisecond duration, and 70 cycles per second.

The stimulation was repeated, with the intensity and duration held constant, at frequencies of 7, 14, 35, and 70 cycles per second.

At a frequency of 7 cycles per second no change in the pulse pressure was noted. At 14 cycles per second, the systolic and diastolic pressure elevated to 120/102 with no alteration in the pulse pressure, but with an increase in the pulse rate to 154 per minute. When the stimulation was applied with a frequency of 35 cycles per second, the systolic and diastolic pressure rose to 190/140 with an increase in the pulse pressure to 50 mm. Hg. and an acceleration of the heart rate to 170 per minute. Reapplying the original stimulus at a frequency of 70 cycles per second, the systolic and diastolic pressures rose to 220/150, a pulse pressure of 70 mm. Hg., and a pulse rate of 192 per minute. The relatively small difference in the response obtained at 35 cycles per second

as compared to 70 cycles per second, indicates that the frequency response curve is approaching a plateau of optimal frequency for stimulation. The curve of the frequency response up to 70 cycles per second is similar to the detailed curves of Peiss (67). It was therefore decided to use a frequency of 70 cycles per second in order to compare the data on the hypothalamus with those on the brain stem.

3. Recording Technique

Records of the pressure pulse in the carotid artery were made by means of a Sanborn Electromanometer adapted to drive a Sanborn EKG optical galvanometer. From the galvanometer mirror a light beam was focused on moving photosensitive paper to give a photokymographic record of the pressure pulse curve.

The general principle of operation is as follows. A closed fluid system is continuous with the transducer, and, in this case, the arterial blood of the carotid artery. The pressure and alterations in pressure in the fluid system is transmitted onto the transducer. The transducer contains a condenser microphone as the variable component of an alternating current bridge circuit. When the condenser-transducer is activated by pressure, the bridge is unbalanced and the output voltage is proportional to the magnitude of change occurring in the variable component.

The output of the electromanometer is then suitably amplified to drive the optical galvanometer. A modified Sanborn Model 126 general purpose amplifier was employed at this stage in the circuit. The modification results in a critically damped galvanometer response to a square wave signal input.

The photokymograph consisted of a Phipps and Bird model 70 - 140 kymograph housed in a light tight metal box. The metal box was provided with a slit $1/4$ inch wide and $1 1/2$ inches long through which the reflected

light beams were focused. By using an appropriate lens system, the light beams from the galvanometer mirror, the timer, and the single magnet were focused on the photosensitive paper. The photosensitive paper could be driven at a variety of speeds by the kymograph. The recording setup is pictured in figure 2.

Experimental Procedure

This study was carried out on 20 young adult cats. The surgical procedures were carried out under local anesthesia (pentothal). The animals

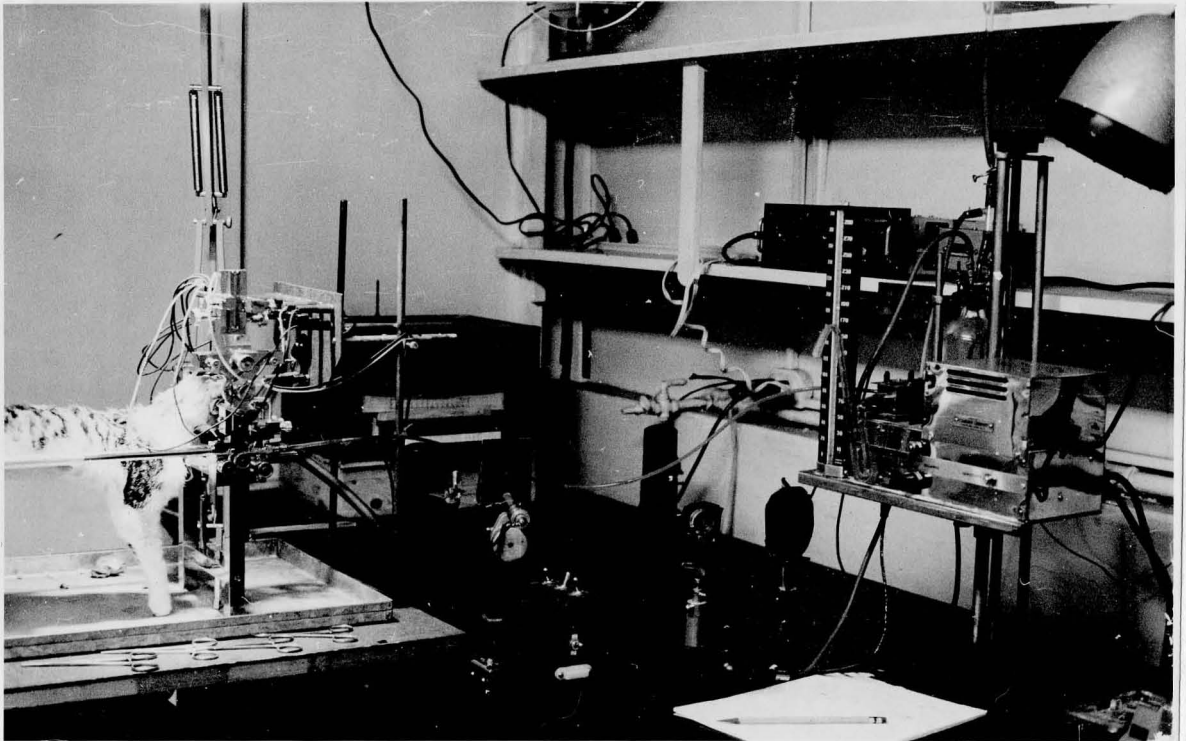


FIGURE 2

The experimental setup.

4. Experimental Procedure

This study was carried out on 28 young adult cats. The surgical procedures were carried out under local anesthesia (procaine). The animals were immobilized with 0.2 mg./Kg. of intravenous d-tubocurarine, and were given supplemental doses of 0.1 mg./Kg. as needed during the course of the experiment. The trachea was cannulated and artificial respiration was instituted. The vagi were exposed and sectioned. The common carotid artery was isolated and cannulated with the appropriate size polyethylene tubing. The polyethylene tubing and the three-way adapter valve, connected to the fluid system of the electromanometer, were filled with heparin solution.

The animal was then placed in the stereotaxic instrument. A small hole was made in the cranium and the stimulating electrodes inserted into the desired area as described above.

The cat was the animal of choice for a number of reasons. The young adult has a relatively uniform skull size. Another advantage is the large volume of neurophysiological and neuroanatomical data that has been obtained from the cat. Several atlases of the cat's brainstem are available in which stereotaxic coordinates are given for the anatomical structures (65).

Animals were sacrificed by disconnecting the respirator. The cranium was removed and the desired section of the brain placed in formalin for histological workup.

5. Analysis of Data

Wiggers (66) demonstrated in artificial circulation models that interpretation of cardiovascular changes could be made from alterations in the pressure pulse tracings. Such studies showed that an increase in heart rate elevates diastolic pressure more than systolic, thus, reducing the pulse pressure; increase in stroke volume raises systolic pressure more than diastolic, thereby increasing the pulse pressure. An increase in peripheral resistance elevates diastolic pressure more than systolic until the arterial distensibility begins to diminish drastically; then, systolic pressure rises progressively faster than diastolic until the pulse pressure actually exceeds normal. Thus, assuming a normal state of arterial distensibility, the pulse pressure will increase as a result of augmented stroke volume and will be reduced by cardiac acceleration and by increased peripheral resistance. Figure 3 illustrates the results of varying each of the parameters that determine pulse pressure.

The dynamics of the artificial circulation scheme are applicable to the intact animal with the realization that the picture is more complex, for the majority of cardiovascular changes obtained are mixed responses.

In the present study, then, the pressure pulse tracing from the photokymograph records were analyzed in the following fashion. A rise in blood pressure with a concomitant rise in diastolic pressure with little or no increase in the pulse pressure or heart rate was interpreted as a vasoconstrictor response. An elevation in the pulse pressure achieved

mainly by a rise in systolic pressure was taken as evidence for an increase in the force of myocardial contraction (augmentor response).

An accelerator response was determined by a shortening of the pulse interval. In order to make an accurate determination of the onset of an accelerator response, the pulse to pulse interval was measured with a caliper from a fast speed record. The first shortening of the pulse interval was taken as the onset of acceleration.

These changes in myocardial function as determined by a pulse analysis are supported in general by a number of recent investigations which attempt to measure more directly the force of myocardial contraction. Cotten (54) stimulated the sympathetic nervous system and directly measured the force of myocardial contraction with strain gauge arches. Rushmer (68) recently reported direct measurements of the change in ventricular size following hypothalamic stimulation in the chronic unanesthetized dog. Randall (70) has demonstrated cardiac augmentation in the isovolumetric heart in situ following direct stellate stimulation.

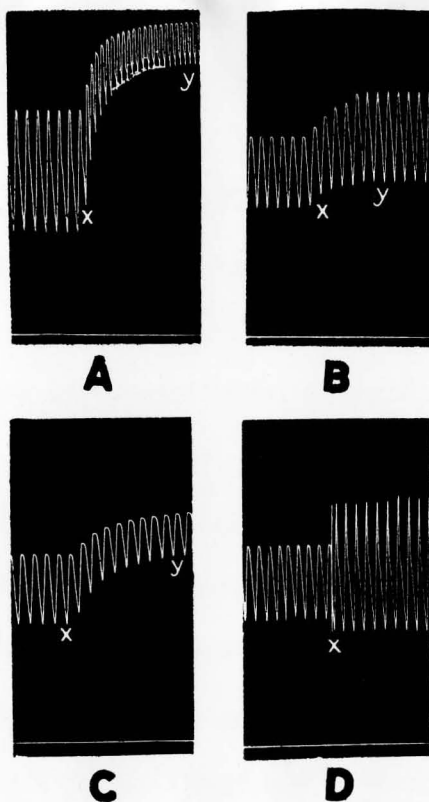


FIG. 7.—Records obtained from artificial circulation model illustrating effects on systolic and diastolic pressure during and after (x-y) alteration of various factors separately. *A*, effect of increasing heart rate; *B*, effect of increasing stroke volume; *C*, effect of increasing peripheral resistance within constant ranges of arterial distensibility; *D*, effect of reducing distensibility of arterial system.

FIGURE 3

Analysis of pulse pressure taken from Wiggers (66), page 15.

EXPERIMENTAL RESULTS

1. Augmentation, Acceleration, and Vasoconstriction Elicited by Hypothalamic Stimulation.

Figures 4 and 5 are schematic sagittal sections one and three millimeters lateral to the midline through the cat's brain. Figure 6 shows two schematic cross-sections through the cat's diencephalon. The sections depicted here are eight and ten millimeters rostral to the interaural line.

The localization of various points represents a composite of a series of 28 animals studied. The open circles represent areas, the stimulation of which resulted in pressor responses. The closed circles represent areas that yielded augmentation in the pulse pressure. The solid triangles are areas that gave augmentation and acceleration of the heart rate upon stimulation. The X's are points of stimulation from which cardiovascular responses could not be elicited.

Over 150 separate points (Horsley-Clarke coordinates) in the posterior diencephalon of the cat have been repeatedly stimulated. Because of this large volume the data are, perhaps, best represented by describing certain types of responses common to a large number of animals. Figures 7,8,9,10, and 11 illustrate the types of responses that were obtained.

SAGITTAL SECTION LATERAL 1 MM.

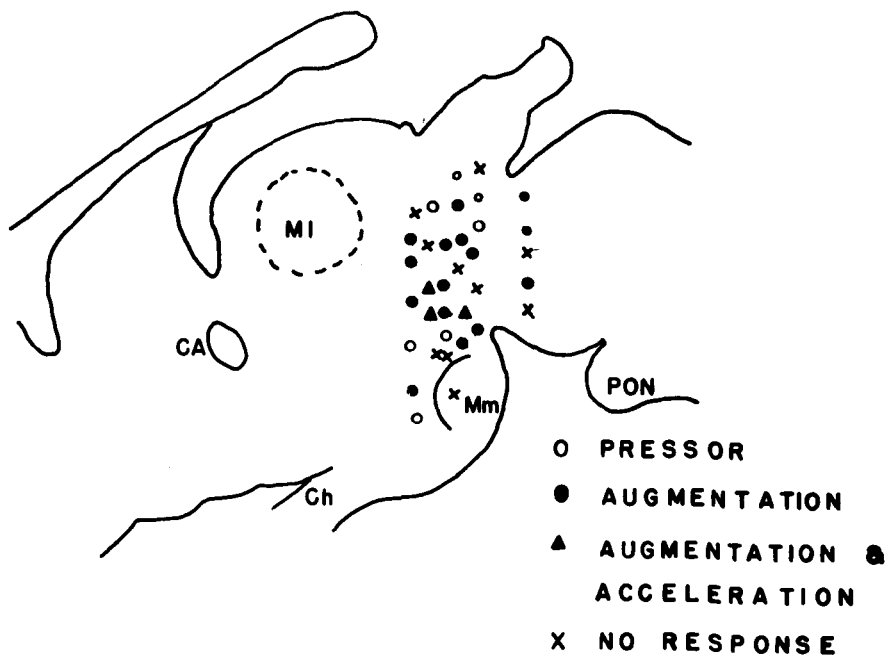


FIGURE 1

A schematic sagittal section 1 millimeter lateral to the midline through the cat's brain.

CA — Commissura anterior

Mm — Corpus mamillare

Ch — Optic chiasma

Pon — Pons

MI — Massa intermedia

SAGITTAL SECTION LATERAL 3 MM.

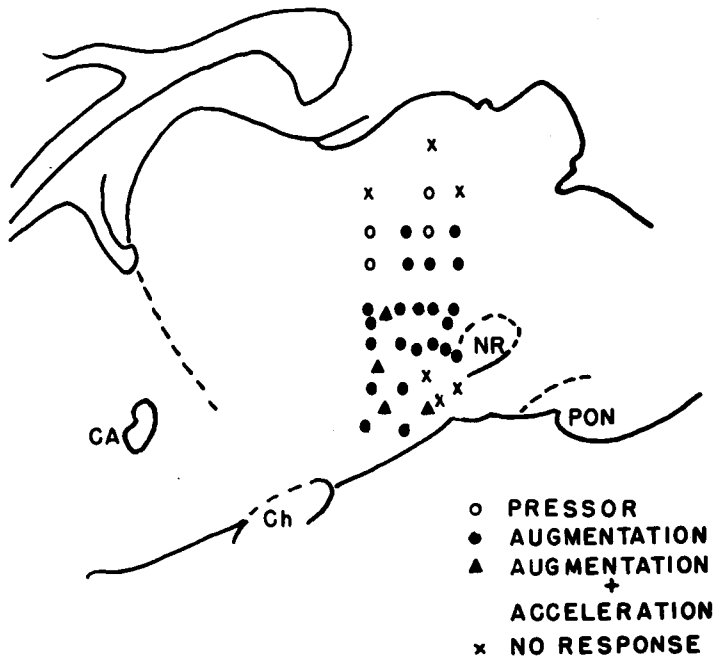


FIGURE 5

A schematic sagittal section three millimeters to the midline through the cat's brain.

CA -- Commissura anterior

NR -- Red Nucleus

Ch -- Optic chiasm

Pon -- Pons

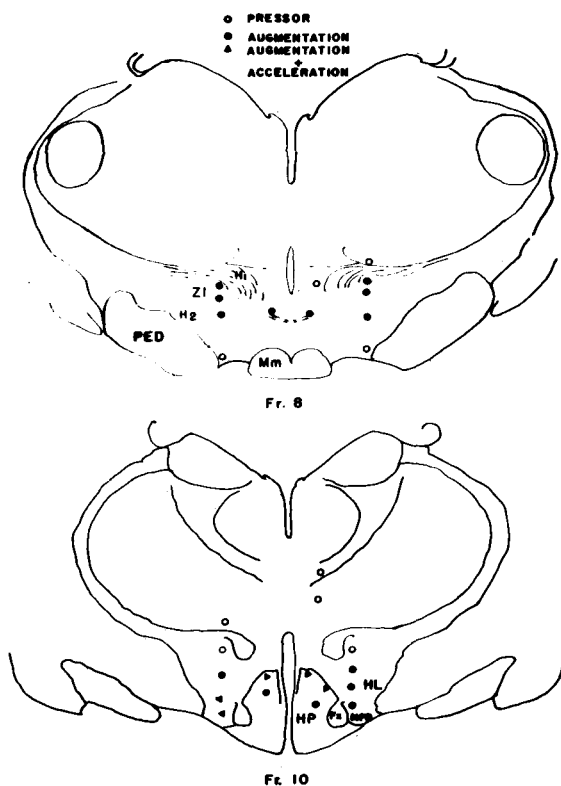


FIGURE 6

Schematic cross-sections through the cat's diencephalon in frontal planes 8 and 10.

- | | |
|---|-------------------------------|
| Fx ——— Fornix | MFB — Median forebrain bundle |
| H ₂ and H ₁ — Fields of Forel | Mm — Corpus mamillare |
| HL ——— Hypothalamus lateralis | PED — Peduncles |
| HP ——— Hypothalamus posterior | ZI — Zona incerta |

The magnitude of these responses exhibited a wide range. In the 28 animals, the range of increase in heart rate varied from approximately 6 per cent to 22 per cent of the control level. The range of increase in pulse pressure varied from 150 per cent to 450 per cent of control. Stimulation of an active point would elevate the mean arterial pressure in some animals as little as 10 mm. Hg. and in others as much as 110 mm. Hg. No depressor responses were ever obtained. This is not an unexpected finding in view of the frequency of stimulation used.

In the figures, the markings of the time line are spaced at one second intervals with a broader marking every ten seconds. The onset and the duration of the stimulus is indicated by the solid interrupted code line. Interruptions in the stimulation signal serve to coordinate the photokymographic record with the written protocol. Its period varied from 7 to 15 seconds. The parameters of the stimulation are given as intensity in volts, duration in milliseconds, and frequency in cycles per second. The point of stimulation is depicted as a black dot in the schematic cross-section of the diencephalon. The stereotaxic coordinates of this point are represented as the number of millimeters rostral to the interaural line, in a frontal plane (A), the number of millimeters lateral to the midline, right lateral (RL) and left lateral (LL), and the number of millimeters dorsal (+) or ventral (-) to the horizontal zero plane (H). The vertical ordinate is blood pressure scaled in increments of 40 mm. Hg.

Stimulation at the point indicated in figures 7 and 8 resulted in an increase in the pulse pressure that is four to five times the control.

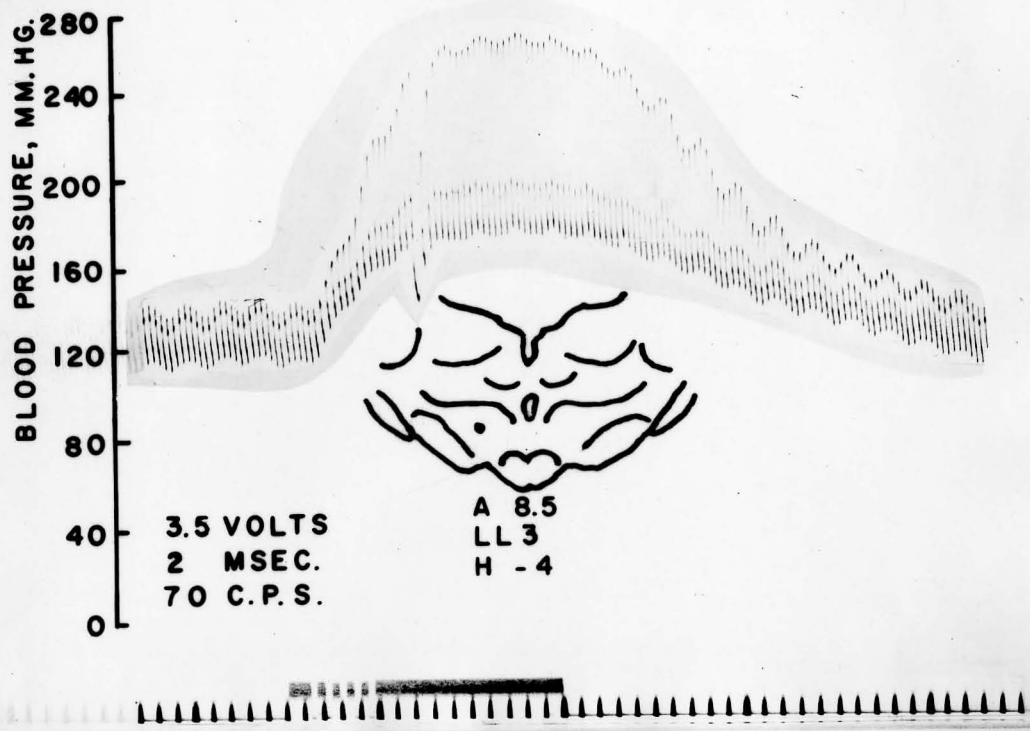


FIGURE 7

Large augmentor response elicited by hypothalamic stimulation.

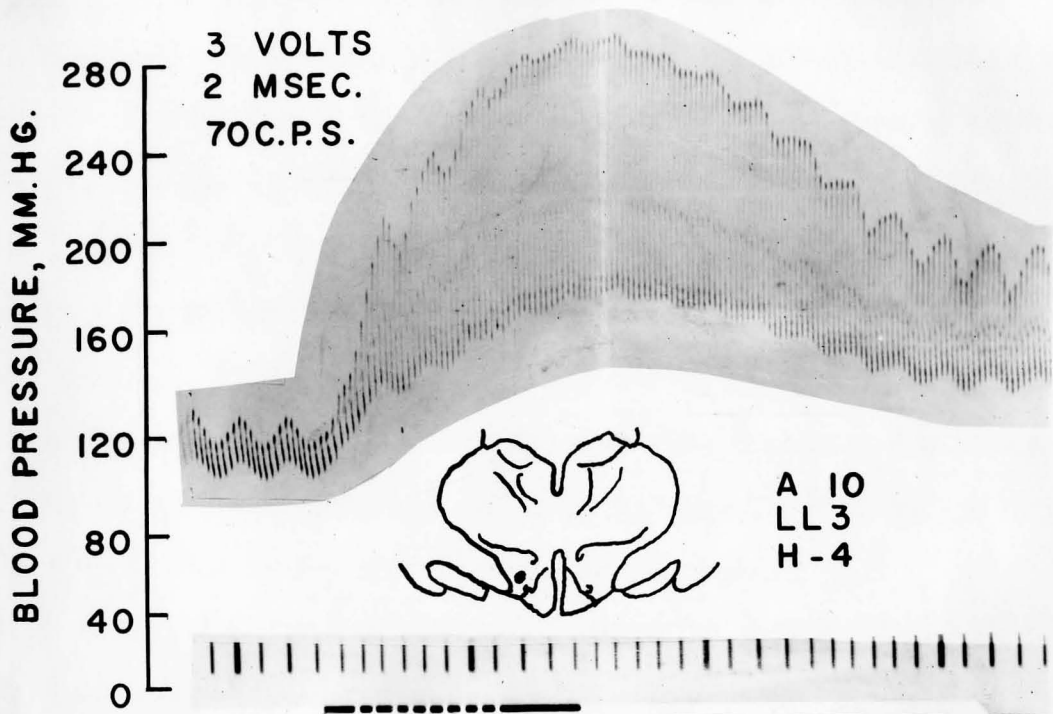


FIGURE 8

Accelerator and large augmentor responses elicited by hypothalamic stimulation.

The point of stimulation in figure 7 was 8.5 mm rostral to the interaural line, 3 mm to the left of the midline, and 4 mm ventral to the horizontal zero plane, or approximately in the H_2 field of Forel. The parameters of stimulation, as shown in the figure, were 3.5 volts, 2 millisecond duration, and 70 cycles per second. The systolic pressure rose from a control level of 142 mm. Hg. to 265 mm. Hg. while the diastolic pressure rose from 115 mm. Hg. to 170 mm. Hg. The pulse pressure increased from a control value of 27 mm. Hg. to 95 mm. Hg., or an increase of 68 mm. Hg. The pulse rate remained constant at 185 beats per minute during the entire procedure. The maximum response as described above was obtained within seven seconds following the onset of stimulation. Within three seconds, or before the tenth beat, there was definite augmentation. The relatively small rise in diastolic pressure was taken as evidence that only a small amount of vasoconstriction accompanied this response.

Figure 8 depicts the effect of stimulation in the area of the median forebrain bundle. The control pulse pressure was 20 mm. Hg. with a systolic pressure of 140 mm. Hg. and a diastolic pressure of 120 mm. Hg. Within 1.2 seconds, or on the fourth beat after the stimulus was applied there was definite increase of the pulse pressure. The full response was achieved in 10 seconds. At this time the pulse pressure had increased to 110 mm. Hg. with a systolic pressure of 295 mm. Hg. and a diastolic pressure of 185 mm. Hg. This was a 450 per cent increase in the pulse pressure.

From the analysis of this response when recorded at a faster

kymographic speed, an elevation in the pulse rate was noted. The heart rate increased from a control value of 240 beats per minute to 255 beats per minute. This is a 6.3 per cent increase in heart rate. A pulse to pulse analysis revealed that the first decrease in the pulse interval occurred 2.4 seconds or on the tenth beat after the onset of stimulation.

Augmentor and accelerator responses from stimulation of other areas are shown in figures 9 and 10. In figure 9 the point of stimulation was in the frontal plane 8.5, in the H_2 field of Forel. On the sixth beat or approximately two seconds after the stimulus was applied the pulse pressure was increased, the full response being obtained within six seconds. The control pulse pressure of 24 mm. Hg. (138/114) increased 2.5 fold to a pulse pressure of 60 mm. Hg. (200/140). No acceleration of the heart rate was noted above the control rate of 168 per minute.

The point of stimulation in figure 10 was the area of the zona incerta, just dorsal to the lateral hypothalamic nucleus. The pulse pressure increased during stimulation to a value 4.5 times the control pulse. Along with this response occurred the largest increase in heart rate which we have obtained by hypothalamic stimulation. The heart rate increased from a control value of 150 per minute to 192 per minute, i.e., an increase of 28 per cent. The latency of onset of this rate change was less than three seconds. With 30 seconds after the cessation of the stimulus the heart rate and diastolic pressure return to a prestimulus level, while the pulse will remain increased for two or three minutes.

Occasionally, responses were obtained in which the systolic and diastolic pressure rose equally. Such a response is shown in figure 11.

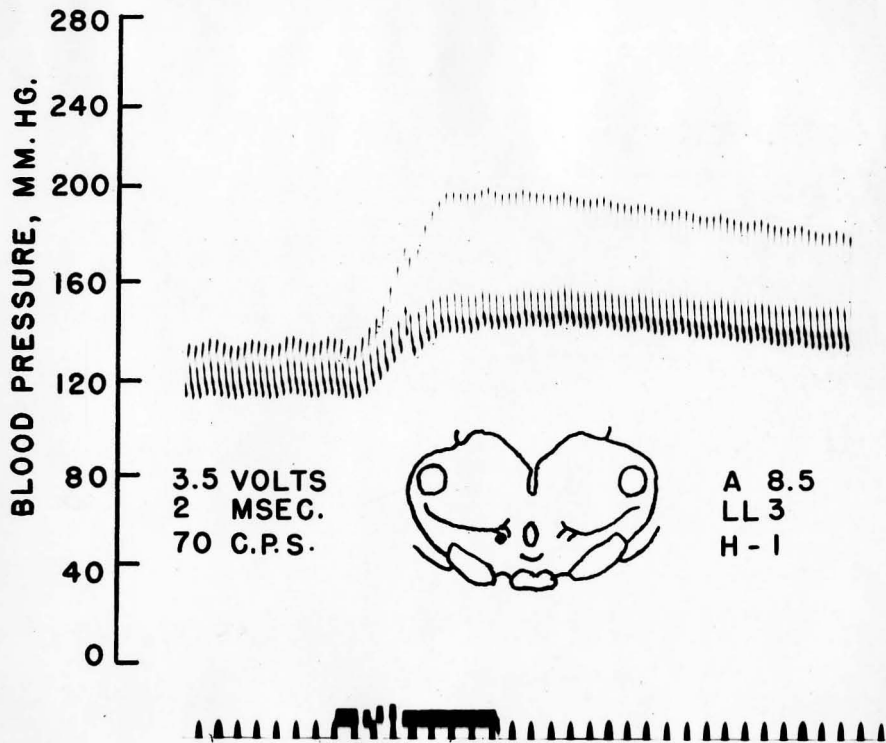


FIGURE 9

Augmentor response elicited by hypothalamic stimulation.

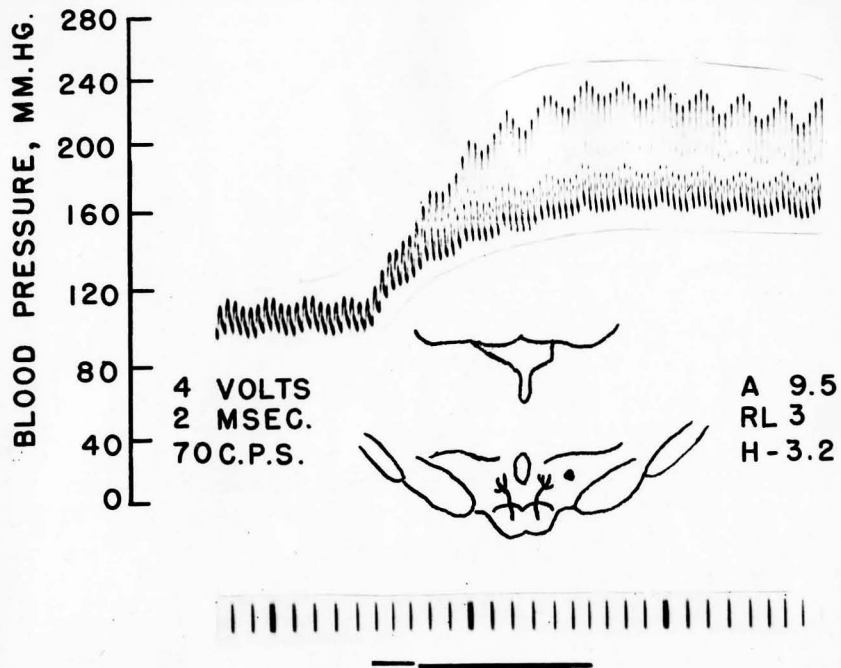


FIGURE 10

Augmentor and large accelerator responses elicited by hypothalamic stimulation.

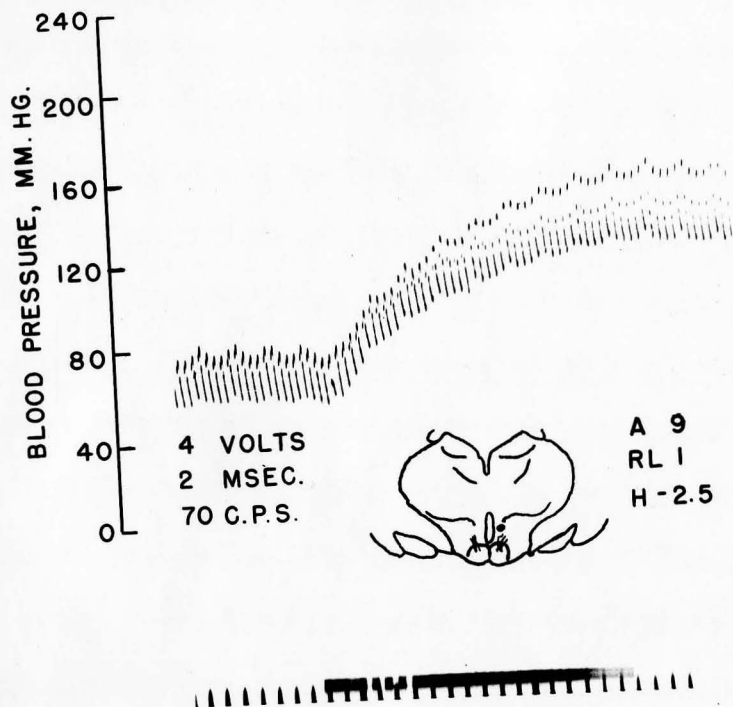


FIGURE 11

Pressor response elicited by hypothalamic stimulation.

The stimulating electrode was located in the lateral hypothalamic nucleus. The systolic pressure rose from a prestimulus level of 80 mm. Hg. to 155 mm. Hg. while diastolic pressure rose from 58 mm. Hg. to 120 mm. Hg. A slight rise in the pulse pressure occurred ten to twelve seconds after the onset of stimulation. The nature of the change in the pressure pulse indicates that the rise in blood pressure was due to an increase in total peripheral resistance, especially since no change in heart rate occurred.

The cardiodynamic changes illustrated above are the result of excitation of the sympathetic outflow to the heart. The alteration in rate cannot be accounted for on the basis of changes in vagal tone, since the vagi were cut. It is important to consider the latency between the onset of the stimulus and the first response of the heart, since augmentation and acceleration of the heart do occur secondary to the activation of the adrenal medulla. Therefore, the interpretation of direct sympathetic activation of the heart has been restricted to those responses that occurred within seven seconds following the application of the stimulus, since this is less than the circulation time of the animals. In all the responses noted, the latencies were in a range of approximately one to four seconds.

The augmentation of myocardial contraction was not the result of changes in peripheral resistance as demonstrated in figures 12 and 13. In three animals the thoracic aorta and the inferior vena cava were occluded with a ligature approximately eight millimeters before they enter the diaphragm. In figure 12, the stimulus was applied to the same point in the hypothalamus of the same animal shown in figure 7. The pulse

pressure recorded 10 minutes before the occlusion was 27 mm. Hg. (142/115). After the occlusion the pulse pressure was 45 mm. Hg. (170/125). After stimulation the pulse pressure increased to 85 mm. Hg. (235/150). Such a procedure also demonstrates that the augmentor responses were not the results of an increased adrenal medullary activity.

In the experiment shown in figure 13, the stellate ganglia were infiltrated with procaine. In the same animal as the previous figure, the aorta and inferior vena cava were occluded as before. It is of interest to note that the heart rate was slower after stellate block. This is the result of loss of tonic sympathetic discharge mediated through the stellate ganglia. The stimulus was applied to the same area as before and the augmentor response was not obtained. Thus, by blocking the major sympathetic outflow to the heart, the hypothalamic augmentor responses cannot be obtained.

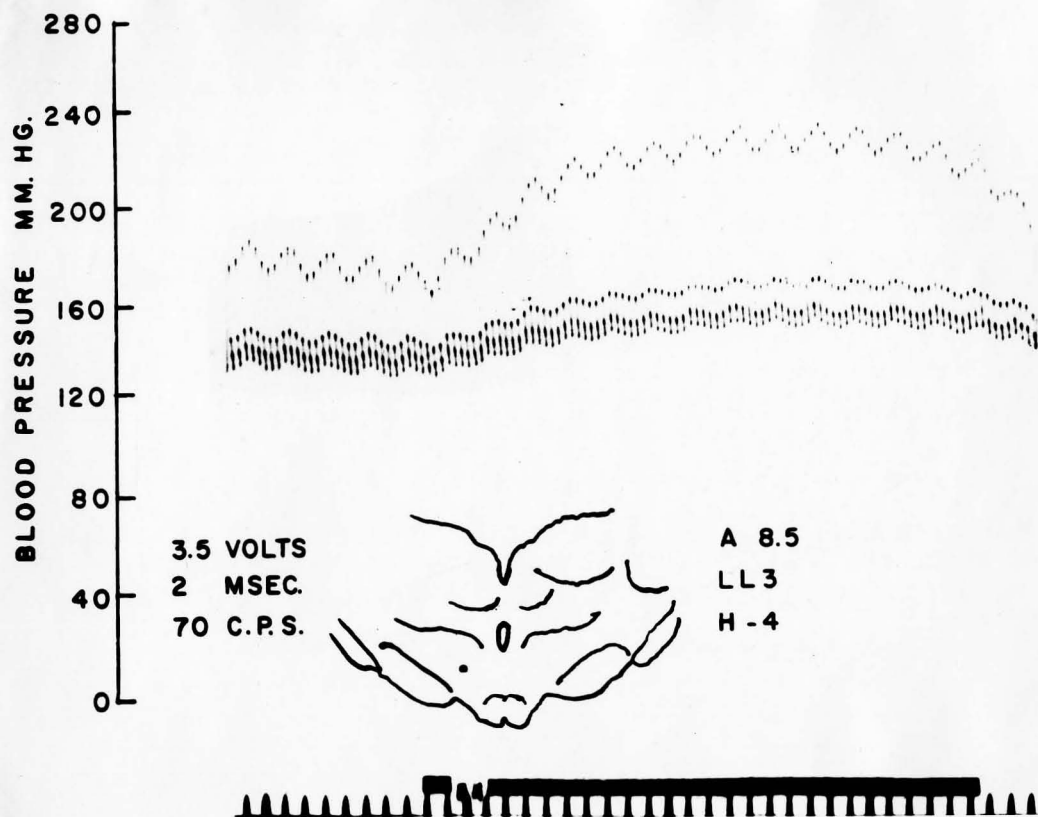


FIGURE 12

Effects of hypothalamic stimulation after the thoracic aorta and inferior vena cava are occluded.

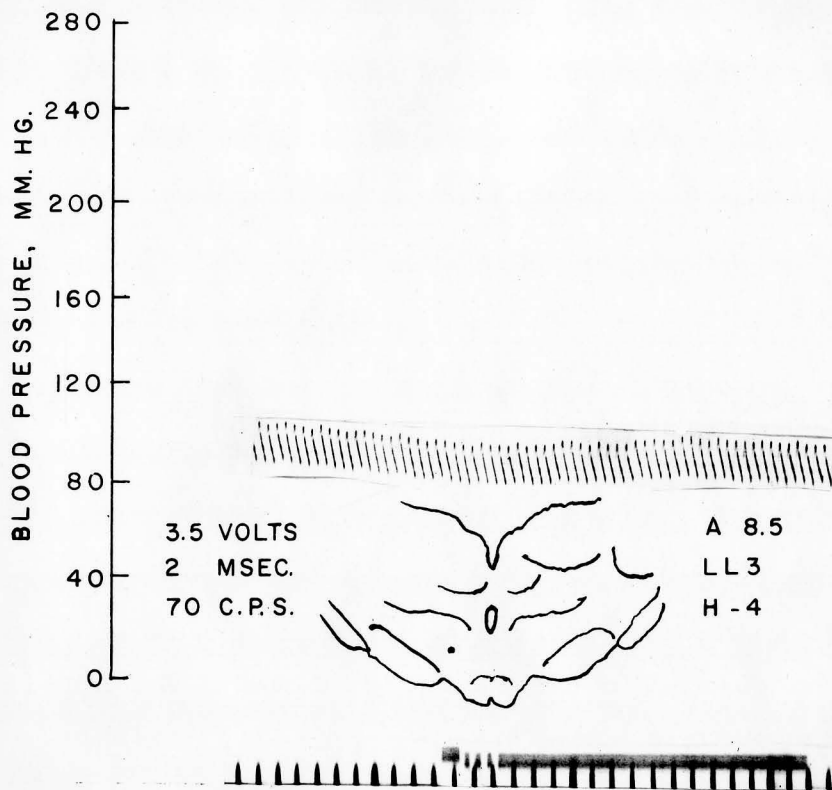


FIGURE 13

Effects of hypothalamic stimulation after the infiltration of the stellate ganglia with procaine.

2. Drug Effects on Vasomotor Responses

A total of 150 different points in the posterior hypothalamus were electrically stimulated in three cats anesthetized with 30 mg./Kg. of Sodium pentobarbital (Nembutal). Hypothalamic stimulation under these conditions was successful in eliciting only a few pressor responses consisting of a maximal rise of 20 mm. Hg. in mean arterial pressure. No acceleration or augmentation of the heart was noted. Hypothalamic responsiveness under Nembutal anesthesia is in striking contrast to that of the vasomotor areas in the medulla, which are relatively unaffected by equivalent doses of Nembutal (61).

To further test the depressant action of Nembutal, the following experiments were performed. Six cats were prepared in the usual manner and an active point in the hypothalamus was located. Stimulation of these points produced cardiovascular changes similar to those described for figures 7,8,9, and 10. Small doses of Nembutal, 2.5 - 10 mg./Kg., were administered either intra-arterially by way of the common carotid artery or intravenously by way of the femoral vein. The active areas were again stimulated and the degree and duration of the depression were measured. It was found that only 2.5 mg./Kg. of Nembutal given intra-arterially was capable of completely depressing the augmentor responses. The duration of hypothalamic depression was found to be a function of the amount of hypnotic given and was dependent upon the route of intravascular injection. For example, the intravenous injection of 10 mg./Kg. of Nembutal completely depressed the hypothalamus. Three and one-half hours elapsed before the

responses had returned to 80 per cent of the predepressed level. It was further noted that subsequent similar doses of the hypnotic were more effective in their action.

An example of this phenomenon is illustrated in figure 14. The open circles represent the actual systolic and diastolic pressure taken from a photokymographic record. During the control stimulation the systolic and diastolic pressure rose with a large augmentation of the pulse. At the arrow, 1/10 of the normal anesthetic dose of Nembutal (3.5 mg./Kg.) was given intra-arterially by way of the carotid artery. The stimulus was repeated 2 minutes following the injection. This stimulation resulted in a small pressor response with little augmentation in the pulse pressure. Within forty minutes after the injection the response had returned to 80 per cent of the predepressed level.

A second set of stimulating electrodes were inserted into the medullary vasomotor area of this cat. Figure 15 illustrates the type of responses obtained on stimulating this area before and after the intra-arterial injection of Nembutal (3.5 mg./Kg.). Although the cardiovascular responses were slightly depressed after the injection, a rise in pulse pressure to 30 mm. Kg. was still obtained. The depressor action lasted for twelve minutes. This is considerable shorter time than that of the hypothalamic depression.

In two cats the injection of 20 mg./Kg. of alpha-chloralose did not alter the ability to obtain cardiovascular responses from the medulla or the hypothalamus. This is supported by other studies on the cat from this laboratory which show that even full anesthetic doses of alpha-chloralose (100mg/Kg.) does not depress responsiveness of the hypothalamus to electrical stimulation.

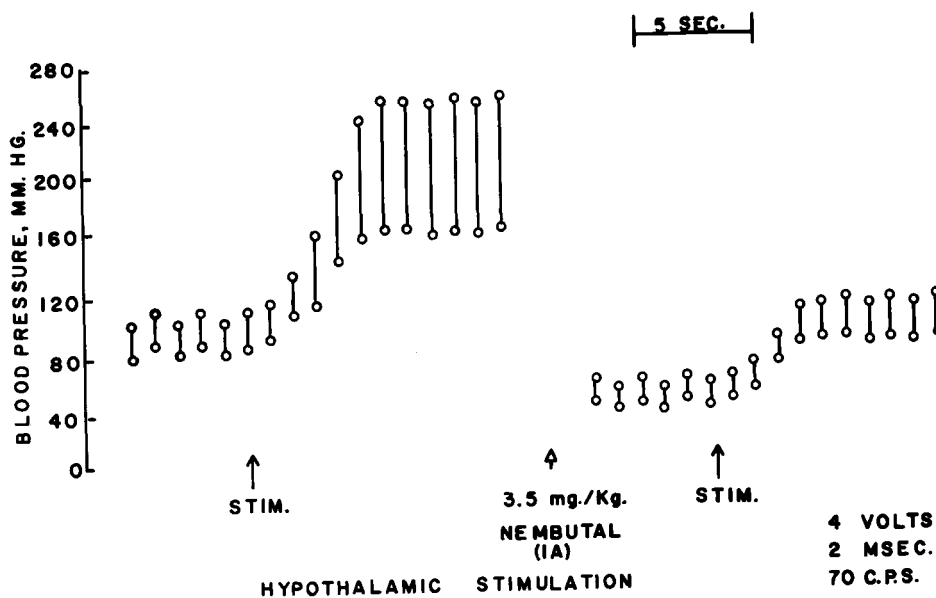


FIGURE 14

Effects of Nembutal on the vasomotor responses elicited by hypothalamic stimulation.

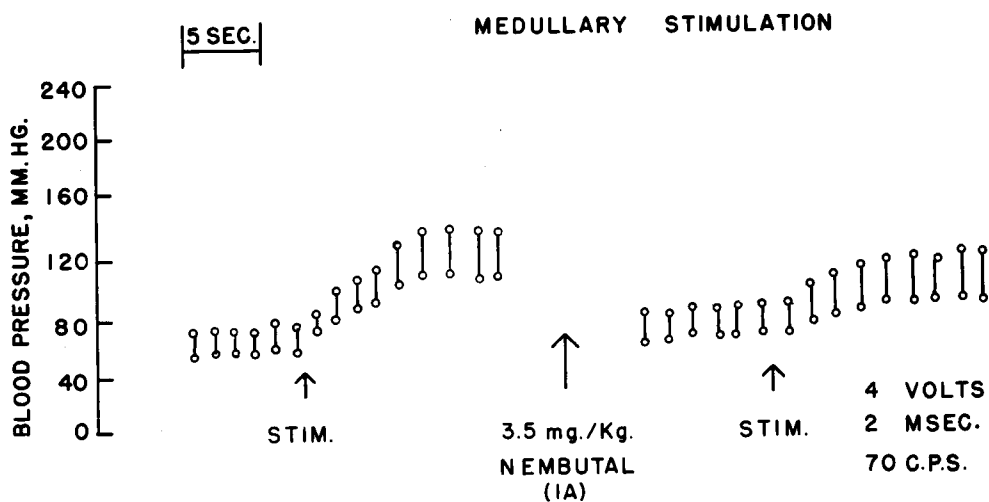


FIGURE 15

Effects of Nembutal on the vasomotor responses elicited by stimulation of the medullary vasomotor area.

DISCUSSION AND CONCLUSIONS

Previous investigators have demonstrated the role of the hypothalamus in modifying sympathetic responses. Their interpretations as to its control over the cardiovascular system were limited chiefly by the recording techniques employed and the anesthetic agent used. This study demonstrates conclusively for the first time that hypothalamic stimulation greatly augments the force of myocardial contraction to give an increase in pulse pressure two to five times the pre-stimulation level.

The increased force of systolic ejection is the result of activation of the sympathetic post-ganglionic outflow to the heart and is not the result of increased adrenal medullary hormonal output. The latter possibility is positively eliminated by the short (1-4 second) latency of the response. Also, when the secretions of the adrenal glands are prevented from reaching the heart by ligating the thoracic aorta and inferior vena cava, the response is still obtained. Evidence is also presented that would tend to exclude the possibility that changes in peripheral resistance could account for the elevated pulse pressure.

This conclusion is further supported by recent work of Rushmer and co-workers (68), who directly measured changes in heart size following hypothalamic stimulation in the chronic unanesthetized dog. It was their conclusion that the cardiac augmentation which occurred with hypothalamic stimulation closely resembles that observed during exercise.

The more dramatic effect seen during hypothalamic stimulation is an augmentation rather than an acceleration of the heart. In only one instance did the pulse rate increase to above 20 per cent of the control level. A number of factors may account for this apparent lack of hypothalamic regulation of heart rate. The only rate changes measured in this work have been those that result from direct sympathetic postganglionic activation of the heart. The vagi are severed resulting in a loss of the effect of vagal influence on the heart. Because of this, the heart rate is faster as a result of dominance of sympathetic tone. A second factor that contributes to an elevated basal heart rate is that the animal is in a conscious state and still has afferent sensory input that may reach a conscious level, and thus influence heart rate. There may be a species difference such that the cat's major physiological mechanism for accelerating the heart is by central inhibition of vagal tone.

The large augmentor responses that obtain with no changes in heart rate are best explained by the differential activation of fibers that terminate on myocardial muscle rather than nodal tissue.

The anatomical location of areas modifying cardiovascular function is in general agreement with the work of others (16,17,26, & 29). The lack of accelerator points in the more caudal portions of the posterior hypothalamus suggests incomplete mapping of this area.

The following conclusions can be made from all animals which showed responsiveness to electrical stimulation of the hypothalamus. There is a broad area, essentially the posterior lateral hypothalamus, limited

rostrally by a plane at the level of the posterior border of the optic chiasma and caudally by a plane at the level of the anterior border of the red nucleus, extending three millimeters lateral on either side of the midline, from which various types of cardiovascular responses were obtained.

In some cats, a given type of response was quite discretely localized, in the sense that a one millimeter movement of the electrode resulted in loss of the response. In some cats, a given response had a much more diffuse representation. An augmentor response could consistently be obtained from an area in the lateral hypothalamic nucleus just dorsal to the median forebrain bundle, but the magnitude of which could not be predicted.

The cardiovascular responses elicited by hypothalamic stimulation are greatly depressed by intravascular injections of Sodium pentobarbital. This is in sharp contrast to the responsiveness to electrical stimulation of the medullary vasomotor areas under the influence of this drug. Recent studies of Peiss (67) have shown that the activity of these medullary areas is depressed by either intravascular or intramedullary injections of amounts of α -tubocurarine small enough to have no demonstrable effects at the myoneural junction. In the present study all of the hypothalamic responses were obtained while the animal was immobilized with α -tubocurarine. This differential drug effect on the two areas of the brain stem suggests that some of the hypothalamic cardiovascular responses may not require the integrity of the medullary vasomotor areas for mediation of their effects.

This conclusion is further supported by an experiment in one

animal. Following the bilateral removal of approximately 2.5 millimeters of the dorsal portion of the medulla oblongata by a frontal section parallel to the floor of the fourth ventricle extending from just caudal to the obex to a midpontine level, stimulation of an active area in the hypothalamus still was capable of producing a response. This response, although reduced in magnitude, produced a rise in the pulse pressure. Such a section removes the most reactive part of the vasomotor areas in the dorsal medulla or the pressor point of Ranson and co-workers (69).

This study suggests a number of possible future investigations related to the hypothalamic control of the cardiovascular system.

A more extensive mapping of reactive regions is needed to delineate those hypothalamic areas associated with changes in heart rate. An attempt should be made to track the efferent descending pathways through the lower brain stem over which these accelerator and augmentor impulses are conducted. The work of Randall and associates (56) shows a differential functional effect on the heart between the right and left sympathetic trunk. The responses obtained from the hypothalamus were bilateral in location. This suggests an uneven decussation of accelerator and augmentor pathways between the hypothalamus and the sympathetic trunk.

By placing discrete electrolytic lesions in the medullary vasomotor area, the necessity of this area in mediating hypothalamic cardiovascular responses may be tested. Recent evidence (61) has shown that accelerator responses are not obtained from the classical vasomotor areas. Instead, changes in the heart rate were found to occur when the more ventro-lateral aspect of the medulla was stimulated. This area is usually thought

to be relatively devoid of cardiovascular activity. Thus, the proposed study could lend evidence in support of separate efferent pathways in the brain stem by which the dynamics of the heart may be altered.

Besides those reported, other changes in the cardiovascular system should be investigated following hypothalamic stimulation. Experiments should be designed to measure the effect of cardiac augmentation on atrial and ventricular filling pressures. The ventricular contractile force could be recorded with a suitable strain gauge arch. This would give a direct measure of the augmented ventricular beat.

SUMMARY

Using stereotaxic procedures a large area of the lateral posterior hypothalamus of 28 unanesthetized, vagotomized cats immobilized with d-tubocurarine was explored with concentric bipolar stimulating electrodes. Surgical procedures were performed under local procaine anesthesia. Analysis of the pressure pulse curves permits an accurate measure of cardiac augmentation and acceleration, when vascular constriction is not a complicating factor. Certain specific areas exert significant control over sympathetic augmentation of myocardial contraction, yielding when stimulated, a pulse pressure increase of two to five times the pre-stimulation value. These responses are accompanied by a small elevation of diastolic pressure and occasionally by a small cardiac acceleration. The responsive regions in the lateral posterior hypothalamus are extremely sensitive to Sodium pentobarbital. Full hypnotic doses greatly elevated the threshold of response, whereas the vasomotor areas in the medulla were relatively unaffected by equivalent doses.

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APPROVAL SHEET

The dissertation submitted by John W. Manning, Jr. has been read and approved by five members of the faculty of the Graduate School.

The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the dissertation is now given final approval with reference to content, form, and mechanical accuracy.

The dissertation is therefore accepted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

May 28, 1958
Date

Clarence W. Pease
Signature of Advisor